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(54) TNF INHIBITORS

TNF-INHIBITOREN

INHIBITEURS DE FACTEUR DE NECROSE TUMORALE

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Description

Field of Invention

The present invention relates to 4-(substituted phenyl) pyrrolidinone derivatives which inhibit the production of Tumor Necrosis Factor (TNF).

Background of the Invention

TNF, a serum glycoprotein, has been implicated in mediating or exacerbating various mammalian conditions such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to he maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and herpes viruses for similar reasons as those noted.

The ability to control the adverse effects of TNF is furthered by the use of the compounds which inhibit TNF in animals who are in need of such use. There remains a need for compounds which are useful in treating TNF mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

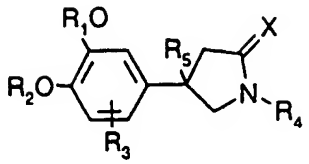
Summary of the Invention

This invention relates to the inhibition of TNF production in an animal, including humans, which comprises administering to an animal in need of such treatment, an effective TNF inhibiting amount of a compound of Formula (I).

This invention also relates to the treatment of a human afflicted with a human immunodeficiency virus (HIV), which comprises administering to such human an effective TNF inhibiting amount of a compound of Formula (I).

This invention also relates to a pharmaceutical composition which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent for use in the treatment of a TNF mediated disease.

The compounds of this invention useful in treating a TNF mediated disease by inhibition or reduction of the *in vivo* levels of TNF are represented by the structure:



FORMULA (I)

wherein:

R_1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-2} alkyl, aryl, aryl C_{1-6} alkyl or a heterocyclic ring, all optionally substituted by one or more halogen atoms or by one substituent group selected from hydroxy, carboxy, C_{1-5} alkoxy, C_{1-5} alkoxycarbonyl, carboxamido, C_{1-5} alkylcarboxamido, C_{1-5} dialkylcarboxamido, carboxy C_{4-7} cyclicamido, amino, C_{1-5} alkylamino, C_{1-5} alkyl, C_{2-5} alkyleneimino, a morpholino or piperazino ring; or R_1 or R_2 together form an alkylene chain of 1-3 carbon atoms;

R_2 is selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl all optionally substituted by one or more halogen atoms;

R_3 is a hydrogen atom or methoxy;

R_4 is a hydrogen atom, C_{1-5} alkyl, aryl, aryl optionally substituted by one or two methyl groups, aralkyl, C_{1-6} alkanoyl or COR_6;

R_6 is C_{1-10} alkyl, hydroxy, O-C_{1-10} alkyl, aryl, aralkyl, O-aryl, O-aryl C_{1-10} alkyl, NH_2, NH-C_{1-10} alkyl, NH-aryl, N(C_{1-10}alkyl)$_2$, N(aryl)$_2$, or -N(aryl)-(C_{1-10}alkyl);

X is an oxygen or sulfur atom;

R_5 is hydrogen or C_{1-4} alkyl; or the pharmaceutically acceptable salts thereof. The compounds are used in the manufacture of a medicament for treating a TNF mediated disease in an animal, with the proviso that said treatment does not include topical treatment of an inflammatory disease, inhalation treatment of allergic airway disorders such as bronchial asthma and rhinitis and the oral and rectal treatment of allergic diseases of the intestinal tract such as ulcerative colitis and colitis granulomatosa.

Detailed Description of the Invention

This invention relates to the inhibition of TNF production in an animal, which comprises administering to an animal in need of such treatment, an effective TNF inhibiting amount of a compound of Formula (I). This may be used for the prophylactic treatment or prevention of certain TNF mediated disease states amenable thereto.

The compounds of Formula (I) are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo. The viruses contemplated for treatment herein are those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to; HIV-1, HIV-2 and HIV-3 as noted above, Epstein Barr (EB) Virus, Human Papilloma Virus, Influenza, Viral Encelphalitis, Respiratory Syncytial virus (RSV), Hepatitis A, Hepatitis B, Hepatitis non A non B, and the Herpes family viruses, including, Cytomegalovirus (CMV), Herpes Varicella Zoster, and Herpes Simplex I & II.

Preferred compounds of Formula (I) of the present invention are those wherein

X is oxygen;
R_1 is selected from C_{1-6}alkyl, C_{3-7} cycloalkyl, or C_{3-7} cycloalkyl - C_{1-4} alkyl;
R_2 is selected from methyl;
R_4 is hydrogen, C_{1-6} alkanoyl, or COR_6;
R_3 is hydrogen; and
R_5 is hydrogen.

More preferred compounds of Formula (I) are those wherein R_1 is C_{3-7} cycloalkyl or C_{1-6} alkyl and R_4 is hydrogen or C_{1-6} alkanoyl. A more preferred embodiment is where R_1 is cyclopentyl or methyl. Most preferred is R_1 as cyclopentyl and R_2 as methyl. Preferrable halo substituent groups are fluorine and chlorine.

Specifically exemplified is 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone.

By the term "C_{1-6}alkyl" or "alkyl" groups as used herein is meant to include both straight or branched chain radicals of 1 to 7 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

By the term "alkenyl" as used herein is meant to include, but not limited to vinyl, 1-propenyl, 2-propenyl, 2-propinyl or 3-methyl-2-propenyl.

By the term "cycloalkyl" or "cycloalkyl alkyl" as used herein is meant to include groups of 3-7 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl or cyclohexyl.

By the term "aryl" or "aralkyl" as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, preferably monocycle, such as phenyl, benzyl, phenethyl or naphthyl.

By the term "heterocyclic ring" as used herein is meant a saturated ring of 5 to 6 members having a single oxygen, sulfur or nitrogen atom, such as, but not limited to 2- and 3-tetrahydropyranyl, 2- and 3-tetrahydrofuranyl, pyrrolidino, 2- and 3-pyrrolidyl, piperidinino, 2-, 3- and 4-piperidyl and the corresponding N-alkyl pyrrolidyl and piperidyl rings wherein the alkyl is of 1-4 carbon atoms. Also encompassed within the scope of this invention are heterocyclic rings having more than one hetero atom such as morpholino, piperazino or N-alkyl piperazino.

By the term "halo" as used herein is meant all halogens, i.e., chloro, fluoro, bromo and iodo.

By the term "inhibiting the production of IL-1" or "inhibiting the production of TNF" is meant

a) a decrease of excessive in vivo IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels by inhibition of the in vivo release of IL-1 by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the translational or transcription level, of excessive in vivo IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of IL-1 or TNF levels as a postranslational event.

By the term "TNF mediated disease or disease states" is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1, or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise. Preferably TNF-α is inhibited.

By the term "cytokine" as used herein is meant any secreted polypeptide that affects the functions of other cells, and is a molecule which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines and lymphokines regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte out many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutraphils, endothelial cells, brain astrocytes, bone marrow stromal cells, epideral keratinocytes, and β-lymphocytes. Lymphokines are generally referred to as being produced by lymphoctye cells. Examples of cytokines for the present invention include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNFα) and Tumor Necrosis Factor beta (TNFβ).

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention.

The preparation of the compounds of Formula (I) can be carried out by one of skill in the art according to the procedures outlined in the Example section, infra, or by Schmiechen et al., U.S. Patent No. 4,012,495, March 5, 1977; Schmiechen et al., U.S. Patent No. 4,193,926, March 18, 1980; Huth et al., U.S. Patent No. 4,153,713, May 8, 1979; Saccomano et al., WO 87/06576 November 5, 1987; and in Marivet et al., J.Med Chem., Vol. 32, pages 1450-57 (1989).

The compounds of Formula (I) wherein R_5 is alkyl may be prepared by analagous methods to those illustrated above, notably U.S. Patent 4,193,926, by using an appropriately substituted alkylphenone (substituted with the appropriate R_5 alkyl group) as opposed to using the benzaldehyde described in the cited patent literature. Alternatively the compounds may be prepared by the processes exemplified in Klose et al., DE 3438839. In DE-A-3438839 the compounds are used for topical treatment of an inflammatory disease, inhalation treatment of allergic airway disorders such as bronchial asthma and rhinitis, and the oral and rectal treatment of allergic diseases of the intestinal tract such as ulcerative colitis and colitis granulomatosa.

The compounds of Formula (I) or a pharmaceutically acceptable salt thereof, can be used in the manufacture of a medicament for the treatment, prophylactically or therapeutically of any disease state in an animal which is exacerbated or caused by TNF production by such animal's cells, such as but not limited to monocytes and/or macrophages, especially caused by excessive or unregulated TNF production. The compounds of Formula (I) are administered in an amount sufficient to inhibit TNF production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate the disease state. Abnormal levels of TNF, for the present invention, constitute levels of 1) free (not cell bound) TNF, greater than or equal to 1 picogram per ml; 2) any cell associated TNF; or 3) the presence of TNF mRNA above basal levels in cells or tissues in which TNF is produced.

There are several disease states in which excessive or unregulated TNF production by monocytes and/or macrophages is implicated in exacerbating and/or causing the disease. These include endotoxemia and/or toxic shock syndrome [See Tracey et al., Nature 330:662-664 (1987); and Hinshaw et al., Circ. Shock 30:279-292 (1990)]; cachexia [See, Dezube et al., Lancet, 335 (8690):662 (1990)]; Adult Respiratory Distress Syndrome where TNF concentration in excess of 12,000 pg/ml have been detected in pulmonary aspirates from ARDS patients. [See, Miller et al., Lancet 2(8665):712-714 (1989). Systemic infusion of recombinant TNF resulted in changes typically seen in ARDS [See, Ferrai-Baliviera et al., Arch. Surg. 124(12):1400-1405 (1989)]; AIDS where viral replication of latent HIV in T-cell and macrophage lines can be induced by TNF [See, Folks et al., PNAS 86:2365-2368 (1989)]. A molecular mechanism for the virus inducing activity is suggested by TNFs ability to activate a gene regulatory protein (NF-kB) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) [See, Osborn et al., PNAS 86:2336-2340 (1989)]. TNF in AIDS associated cachexia is suggested by elevated serum TNF and high levels of spontaneous TNF production in peripheral blood monocytes from patients [See, Wright et al., J. Immunol. 141(1):99-104 (1988)]. TNF in Bone Resorption Diseases, including arthritis, wherein it has been determined that when activated, leukocytes will produce a bone-reasorbing activity, and data suggests that TNF-α and TNF-β both contribute to this activity. [See e.g., Bertolini et al., Nature 319:516-518 (1986) and Johnson et al., Endocrinology 124(3):1424-1427(1989)]. It has been determined that TNF stimulates bone resorption and inhibits bone formation in vitro and in vivo through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNF may be involved in many bone resorption diseases, including arthritis, the most compelling link with disease is the association between production of TNF by tumor or host tissues and malignancy associated hypercalcemia [See, Calci. Tissue Int. (US) 46(Suppl.):S3-10 (1990)]. In Graft versus Host Reaction, increased serum TNF levels have been associated with major complication following acute allogenic bone marrow transplants [See, Holler et al., Blood, 75(4):1011-1016(1990)]; cerebral malaria, which is a lethal hyperacute neurological syndrome associated with high blood levels of TNF and is the most severe complication occurring in malaria patients. A form of experimental cerebral malaria (ECM) that reproduces some features of the human disease was prevented in mice by administration of an anti-TNF antibody. [See, Grau et al., Imm. Review 112:49-70 (1989)]. Levels of serum TNF correlated directly with the severity of disease and prognosis in patients with acute malaria attacks [See Grau et al., N. Engl. J. Med. 320(24):1586-1591 (1989)]. Another disease state in which TNF plays a role is the area of chronic Pulmonary Inflammatory Diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNF completely blocked the silica-induced lung fibrosis in mice [See Piguet et al., Nature, 344:245-247 (1990)]. High levels of TNF production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis [See Bissonnette et al., Inflammation 13(3):329-339 (1989)]. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNF as compared with macrophages from normal donors [See Baughman et al., J. Lab. Clin. Med. 115(1):36-42 (1990)]. TNF is also implicated in another acute disease state such as the inflammatory response which follows reperfusion, called Reperfusion Injury and is a major cause of tissue damage after loss of blood flow [See, Vedder et al., PNAS 87:2643-2646 (1990)]. TNF also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin [See, Sherry et al., J. Cell Biol. 107:11269-1277 (1988)]. TNF also has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF-induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells [See, Munro et al., Am. J. Path. 135(1):121-132 (1989)].

The method of treatment and monitoring for an HIV-infected human manifesting immune dysfunction or cytokine-mediated disease associated problems is taught in Hanna, WO 90/15534, December 27, 1990. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF activity for other TNF mediated disease states by the compounds of Formula (I). Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia such as levels of reverse transcriptase or viral proteins, and/or for progression of monokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is seen following the normal treatment regimen, then the amount of the monokine activity interfering agent administered is

increased, e.g., by fifty percent per week.

The compounds of Formula (I) may be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNF production, respectively, such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflamed joints, pyresis and pain, with the proviso that said treatment does not include topical treatment of an inflammatory disease.

More preferably the compounds of Formula (I) are useful in the treatment of TNF mediated disease states such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

In addition, the present invention attributes many of the biological disease states attributable to interleukin-1 (IL-1) activity as being attributable to that of TNF activity as well. A comprehensive listing of IL-1 activities can be found in Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985). It should be noted that some of these effects have been described by others as indirect effects of IL-1.

Interleukin-1 (IL-1) has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels. These disease states are also considered appropriate disease states of TNF activity and hence compounds of Formula (I) are also useful in their treatment as well, and the use of the compounds of Formula (I) should not be considered solely limited to the specifically described TNF mediated disease states herein. The compounds of the present invention should be efficacious in an IL-1 mediated disease state as TNF and IL-1 act in a synergistic manner. TNF as well mediates the release, in some instances, of the monokine IL-1, therefore a reduction in the levels of TNF may be useful in the treatment of a disease state wherein IL-1 is a major component.

The present invention therefore, relates to an effective, TNF production inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, useful in treating, prophylactically or therapeutically, any disease state in a human which is exacerbated or caused by excessive or unregulated TNF production. Also the present invention relates therefore, to an effective, TNF production inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof is useful in treating, prophylactically or therapeutically, any disease state in a human which is exacerbated or caused by excessive or unregulated IL-1 production , i.e. where IL-1 is a major component, by such human's monocytes and/or macrophages. Said treatment does not include topical treatment of an inflammatory disease, inhalation treatment of allergic airway disorders such as bronchial asthma and rhinitis, and the oral and rectal treatment of allergic diseases of the intestinal tract such as ulcerative colitis and colitis granulomatosa.

The pharmaceutical composition of the present invention will comprise an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent. The compounds of Formula (I) as used herein, are administered in conventional dosage forms prepared by combining a compound of Formula (I) in an effective amount sufficient to produce the desired activity, respectively, with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed can be readily determined by one of skill in the art who will recognize that such determination will depend upon various well-known factors such as the nature, quantity and character of the particular monokine activity interfering agent being employed and the form and route of administration desired. The carriers employed may be those described elsewhere herein.

The methods of this particular invention, for treating a viral infection, including an HIV-infected individual, may be carried out by delivering the TNF inhibiting compound of Formula (I), topically.

By topical administration herein is meant non-systemic administration and includes the application of a TNF interfering agent externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

Compounds of Formula (I) and their pharmaceutically acceptable salts (when possible), some of which are orally active, can be employed in a wide variety of pharmaceutical forms. The preparation of a pharmaceutically acceptable salt will be determined by the nature of the compound itself, and can be prepared by conventional techniques readily available to one skilled in the art. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 gram. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule

any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavoring or coloring agent.

The amount of a compound of Formula (I) required for therapeutic effect on administration will, of course, vary with the compound chosen, the nature and severity of the condition and the animal undergoing treatment, and is ultimately at the discretion of the physician.

The term 'parenteral' as used herein includes intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may he prepared by conventional techniques.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil. The daily dosage regimen for inhibition of TNF production, via parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The compounds of Formula (I) may be administered orally. Each dosage unit for oral administration contains suitably from 1 mg to 100 mg, and preferably from 10 mg to 30 mg of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 100 mg/Kg, preferably 0.01 to 40 mg/Kg of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit antiinflammatory activity.

The compounds of Formula (I) may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage regimen for a compound of Formula (I) for intranasal administration and oral inhalation is suitably about 0.1 to about 1200 mg.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration. By topical administration is meant non-systemic administration and includes the application of a compound of Formula (I) externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream.

A suitable dose of a TNF production inhibiting compound of Formula (I) is 0.001 mg to about 100 mg of base for topical administration, the most preferred dosage being about 0.01 mg to about 30 mg, for example, 0.003 mg to 10 mg administered two or three times daily.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to

those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as prolylene glycol or macrogols. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic sulfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient, (a compound of Formula (I)) with which it is to be combined, the route of administration and other well-known variables.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

UTILITY EXAMPLES

Example A

Inhibitory Effect of compounds of Formula (I) on in vitro TNF production by Human Monocytes

The inhibitory effect of compounds of Formula (I) on in vitro TNF production by Human Monocytes can be determined by the protocol as described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

Inhibition of LPS-Induced Human Monocyte TNF Production by 4-[(3-Cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone demonstrated an IC_{50}(mM) of 0.15.

UTILITY EXAMPLE B

Two models of endotoxin shock have been utilized to determine in vivo TNF activity for the compounds of Formula (I). The protocol used in the models is described in in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990. These two models, the P. acnes/LPS model and LPS/GAL model, protection from the lethal effects of endotoxin shock is provided by the compound 4-[(3-Cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone (herein called Compound) which showed reduction of the in vivo level of tumor necrosis factor (TNF).

The data shown herein demonstrate that the compounds of the present invention inhibit TNF production in a mammal. Therefore, the compounds of the present invention are useful in inhibiting the production of tumor necrosis factor (TNF) by monocytes or macrophages in a human.

SYNTHETIC EXAMPLES

Example 1

4-[(3-Cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone

a) 3-Cyclopentyloxy-4-methoxybenzaldehyde. A mixture of 3-hydroxy-4-methoxybenzaldehyde (100 grams (g hereinafter), 0.66 moles (mol hereinafter)), potassium carbonate (100 g, 0.73 mol) and bromocyclopentane (80 miliLiters (mL hereinafter), 0.79 mol) in dimethylformamide (0.5 Liters (L hereinafter)) was heated under an argon atmosphere at 100°Centigrade (C hereinafter). After 22 hours (h hereinafter), additional bromocyclopentane (10 mL, 0.1 mol) and potassium carbonate (20 g, 0.14 mol) were added and heating was continued for 24 h. The mix-

ture was allowed to cool and was filtered. The filtrate was concentrated under reduced pressure and the residue was partitioned between ether and aqueous sodium carbonate. The organic extract was washed with aqueous sodium carbonate and dried (potassium carbonate). The solvent was removed in vacuo and the residue was purified by flash chromatography, eluting with 2:1 hexanes/ether to provide a pale yellow oil (121 g, 84%).

Analysis Calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found:
C 70.71, H 7.33.

b) Dimethyl (3-Cyclopentyloxy-4-methoxybenzylidene)malonate. To a solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (66.1 g, 0.3 mol) in toluene (100 mL) under an argon atmosphere was added piperidine (1.5 mL, 15 mmol) and acetic acid (0.85 mL, 15 mmol). The resulting mixture was heated at reflux with azeotropic removal of water for 6 h, then allowed to cool to room temperature. The solvent was removed in vacuo and the residue was partitioned between ether and saturated aqueous sodium carbonate. The organic extract was dried (potsssium carbonate) and the solvent removed in vacuo to provide an orange oil (101 g) which was used without purification.

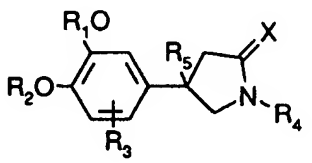
c) Methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate. To a solution of dimethyl (3-cyclopentyloxy-4-methoxy- benzylidene)malonate (25 g, 0.075 mol) in methanol (150 mL) was added a solution of potassium cyanide (4.9 g, 0.075 mmol) in water (20 mL). The mixture was heated at 65-70°C under an argon atmosphere for 6 h, cooled to room temperature and carefully acidified to pH 3 with hydrochloric acid. The liquids were removed in vacuo and the residue was partitioned between ether and aqueous sodium bicarbonate. The ether layer was dried, the solvent removed in vacuo and the residue was purified by flash chromatography, eluting with 20% ethyl acetate/hexanes to provide a solid (14.6 g, 64%): m.p. 69-71°C.

d) 4-[3-Cylcopentyloxy-4-methoxy-phenyl]-2-propionate To a solution of methyl 3-cyano-3-(3-cyclopentyloxy-4-methoxy-phenyl)-propionate (10.2 g, 34 mmol) in methanol (200 mL) was added 70% perchloric acid (4 mL) and 10% palladium on activated carbon (2 g). The resulting mixture was hydrogenated at 60 psi hydrogen for 1 h and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was partitioned between methylene chloride and aqueous sodium carbonate and the methylene chloride layer was dried (potassium carbonate). Solvent removal provided the amine as an oil (10.9 g). This oil in toluene (130 mL) containing sodium cyanide (42 mg) under an argon atmosphere was heated at gentle reflux for 17 h. The solvent was removed in vacuo and the mixture was partitioned between dilute hydrochloric acid and methylene chloride. The organic layer was dried (potassium carbonate), the solvent was removed in vacuo and the residue was recrystallized from methylene chloride/ether to provide a solid (8.4 g, 90%): m.p. 130-131°C.

Analysis Calc. for $C_{16}H_{21}NO_3$: C 69.79, H 7.69, N 5.09; found: C 69.90, H 7.72, N 5.15.

Claims

1. Use of a compound of Formula (I)



FORMULA (I)

wherein:

R_1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-2} alkyl, aryl, aryl C_{1-6} alkyl or a heterocyclic ring, all optionally substituted by one or more halogen atoms or by one substituent group selected from hydroxy, carboxy, C_{1-5} alkoxy, C_{1-5} alkoxycarbonyl, carboxamido, C_{1-5} alkylcarboxamido, C_{1-5} dialkyl-carboxamido, carboxy C_{4-7} cyclicamido, amino, C_{1-5} alkylamino, C_{1-5} alkyl, C_{2-5} alkyleneimino, a morpholino or piperazino ring; or R_1 or R_2 together form an alkylene chain of 1-3 carbon atoms;

R_2 is selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl all optionally substituted by one or more halogen atoms;

R_3 is a hydrogen atom or methoxy;

R_4 is a hydrogen atom, C_{1-5} alkyl, aryl, aryl optionally substituted by one or two methyl groups, aralkyl, C_{1-6} alkanoyl or COR_6;

R_6 is C_{1-10} alkyl, hydroxy, O-C_{1-10} alkyl, aryl, aralkyl, O-aryl, O-aryl C_{1-10} alkyl, NH_2, NH-C_{1-10} alkyl, NH-aryl, $N(C_{1-10}alkyl)_2$, $N(aryl)_2$, or -N(aryl)-(C_{1-10}alkyl);

X is an oxygen or sulfur atom;

R_5 is hydrogen or C_{1-4} alkyl; or the pharmaceutically acceptable salts thereof; in the manufacture of a medicament for treating a TNF mediated disease in an animal, with the proviso that said treatment does not include topical treatment of an inflammatory disease, inhalation treatment of allergic airway disorders such as bronchial asthma and rhinitis and the oral and rectal treatment of allergic diseases of the intestinal tract such as ulcerative colitis and colitis granulomatosa.

2. A use according to claim 1 wherein the TNF mediated disease is selected from septic shock, endotoxic shock, gram negative sepsis, or toxic shock syndrome.

3. A use according to claim 1 wherein the TNF mediated disease is selected from acute immune deficency syndrome (AIDS), AIDS Related Complex (ARC) or any other disease state associated with an HIV infection, cachexia, cachexia secondary to AIDS, or cachexia secondary to cancer.

4. A use according to claim 1 wherein the TNF mediated disease is selected from cerebral malaria, a CMV viral infection, influenza viral infection, or herpes viral infection.

5. A use according to claim 1 wherein the TNF mediated disease is selected from adult respiratory distress syndrome, allograft rejection, or a bone resorption disease.

6. A use according to claim 1 wherein the TNF mediated disease is a topical disease state mediated by excessive TNF production.

7. A use according to claim 1 wherein the TNF mediated disease is selected from: rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflamed joints, pyresis and pain.

8. A use according to any one of claims 1 to 7 wherein R_1 is C_{3-7} cycloalkyl or C_{1-6} alkyl.

9. A use according to any one of claims 1 to 8 wherein R_2 is C_{1-6} alkyl and R_4 is hydrogen, phenyl, benzyl, or COR_6.

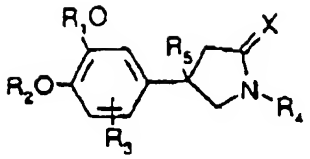
10. A use according to any one of claims 1 to 9 wherein R_2 is methyl R_5 is hydrogen and X is oxygen.

11. A use according to any one of claims 1 to 10 where the compound is 4[3-cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone.

12. A use according to any one of claims 1 to 11 wherein the compound is orally administrable.

Patentansprüche

1. Verwendung einer Verbindung der Formel (I)



(I)

worin

R_1 ausgewählt ist aus C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{3-7}-Alkinyl, C_{3-7}-Cycloalkyl, C_{3-7}-Cycloalkyl-C_{1-2}-alkyl, Aryl, Aryl-C_{1-6}-alkyl oder einem heterocyclischen Ring, wobei gegebenenfalls alle Reste substituiert sind mit einem oder mehreren Halogenatomen oder einer Substituentengruppe, ausgewählt aus Hydroxy, Carboxy, C_{1-5}-Alkoxy, C_{1-5}-Alkoxycarbonyl, Carboxamid, C_{1-5}-Alkylcarboxamid, C_{1-5}-Dialkyl-carboxamid, Carboxy-C_{4-7}-cycloamid, Amino, C_{1-5}-Alkylamino, C_{1-5}-Alkyl, C_{2-5}-Alkylenimin, einem Morpholin-oder Piperazinring; oder R_1 oder R_2 zusammen eine Alkylenkette von 1 bis 3 Kohlenstoffatomen bilden;
R_2 ausgewählt ist aus C_{1-4}-Alkyl, C_{2-4}-Alkenyl, C_{2-4}-Alkinyl, wobei gegebenenfalls alle Reste durch ein oder mehrere Halogenatome substituiert sind;
R_3 ein Wasserstoffatom oder Methoxy ist;
R_4 ein Wasserstoffatom, C_{1-5}-Alkyl; Aryl, Aryl gegebenenfalls substituiert durch eine oder zwei Methylgruppen, Aralkyl, C_{1-6}-Alkanoyl oder COR_6 ist;
R_6 C_{1-10}-Alkyl, Hydroxy, O-C_{1-10}-Alkyl, Aryl, Aralkyl, O-Aryl, O-Aryl-C_{1-10}-alkyl, NH_2, NH-C_{1-10}-Alkyl, NH-Aryl, N(C_{1-10}-Alkyl)$_2$, N(Aryl)$_2$, oder -N(Aryl)-(C_{1-10}-alkyl) ist;
X ein Sauerstoff- oder Schwefelatom ist;
R_5 Wasserstoff oder C_{1-4}-Alkyl ist; oder die pharmazeutisch verträglichen Salze davon;
zur Herstellung eines Medikamentes zur Behandlung einer beim Tier durch TNF ausgelösten Krankheit, mit der Maßgabe, daß die Behandlung nicht eine topische Behandlung einer Entzündungskrankheit, eine Inhalationsbehandlung von Allergie verursachten Atemwegserkrankungen, wie Bronchialasthma und Rhinitis, und die orale und rektale Behandlung vor Allergieerkrankungen des Intestinaltraktes wie Colitis ulcerosa und Colitis granulomatosa einschließt.

2. Verwendung gemäß Anspruch 1, wobei die durch TNF ausgelöste Krankheit ausgewählt ist aus septischem Schock, Endotoxinschock, Gram-negativ Sepsis und toxischem Schocksyndrom.

3. Verwendung gemäß Anspruch 1, wobei die durch TNF ausgelöste Krankheit ausgewählt ist aus akuter Immuninsuffizienz (AIDS), AIDS Related Complex (ARC) oder irgendeinem anderen Krankheitszustand in Verbindung mit einer HIV-Infektion, Cachexie, AIDS-begleitender Cachexie, und Krebs begleitender Cachexie.

4. Verwendung gemäß Anspruch 1, wobei die durch TNF ausgelöste Krankheit ausgewählt ist aus zerebraler Malaria, einer CMV-Virusinfektion, Influenzavirusinfektion und Herpesvirusinfektion.

5. Verwendung gemäß Anspruch 1, wobei die durch TNF ausgelöste Krankheit ausgewählt ist aus ARDS-Schocklunge, Allotransplantationsabstoßung und Knochenresorptionserkrankung.

6. Verwendung gemäß Anspruch 1, wobei die durch TNF ausgelöste Krankheit ein durch TNF-Überproduktion ausgelöster örtlicher Krankheitszustand ist.

7. Verwendung gemäß Anspruch 1, wobei die durch TNF ausgelöste Krankheit ausgewählt ist aus rheumatoider Arthritis, Spondylarthritis, Osteoarthrose, Gichtarthtitis und anderen arthritischen Erkrankungen, entzündeten Gelenken, Pyresis und Schmerz.

8. Verwendung gemäß einem der Ansprüche 1 bis 7, wobei R_1 C_{3-7}-Cycloalkyl oder C_{1-6}-Alkyl ist.

9. Verwendung gemäß einem der Ansprüche 1 bis 8, wobei R_2 C_{1-6}-Alkyl und R_4 Wasserstoff, Phenyl, Benzyl oder COR_6 ist.

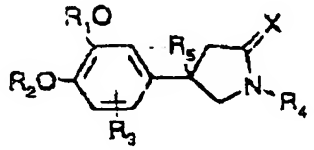
10. Verwendung gemäß einem der Ansprüche 1 bis 9, wobei R_2 Methyl, R_5 Wasserstoff und X Sauerstoff ist.

11. Verwendung gemäß einem der Ansprüche 1 bis 10, wobei die Verbindung 4-[3-Cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinon ist.

12. Verwendung gemäß einem der Ansprüche 1 bis 11, wobei die Verbindung oral verabreicht wird.

Revendications

1. Utilisation d'un composé de formule (I)



FORMULE (I)

dans laquelle :

R_1 est choisi entre des groupes alkyle on C_1 à C_6, alcényle en C_2 à C_6, alcynyle en C_3 à C_7, cycloalkyle en c_3 à C_7, (cycloalkyle en C_3 à C_7)-(alkyle en C_1 ou C_2), aryle, aryl-(alkyle et C_1 à C_6) et un noyau hétérocyclique, tous facultativement substitués avec un ou plusieurs atomes d'halogènes ou avec un substituant consistant en un groupe choisi entre des groupes hydroxy, carboxy, alkoxy en C_1 à C_5, (alkoxy en C_1 à C_5)-carbonyle, carboxamido, (alkyle en C_1 à C_5)-carboxamido, di-(alkyle en C_1 à C_5)-carboxamido, carboxy-(amido cyclique en C_4 à C_7), amino, alkylamino en C_1 à C_5, alkyle en C_1 à C_5, alkylène-imino en C_2 à C_5, un noyau morpholino et un noyau pipérazino ; ou bien R_1 et R_2, coinjointement, forment une chaîne alkylène ayant 1 à 3 atomes de carbone ;
R_2 est choisi entre des groupes alkyle an C_1 à C_4, alcényle en C_2 à C_4 et alcynyle en C_2 à C_4, tous facultativement substitués avec un ou plusieurs atomes d'halogènes ;
R_3 représente un atome d'hydrogène ou un groupe méthoxy ;
R_4 représente un atome d'hydrogène, un groupe alkyle en C_1 à C_5, aryle, aryls facultativement substitué avec un ou deux groupes méthyle, aralkyle, alcanoyle en C_1 à C_6 ou COR_6 ;
R_6 représente un groupe alkyle en C_1 à C_{10}, hydroxy, O-alkyle en C_1 à C_{10}, aryle, aralkyle, O-aryle, O-aryl-(alkyle en C_1 à c_{10}), NH_2, NH-alkyle en C_1 à C_{10}, NH-aryle, N-(alkyle en C_1 à C_{10})$_2$, N-(aryle)$_2$ ou -N-(aryle)-(alkyle en C_1 à C_{10}) ;
X représente un atome d'oxygène ou de soufre ;
R_5 représente l'hydrogène ou un groupe alkyle en C_1 à C_4 ; ou ses sels pharmaceutiquement acceptables ; dans la production d'un médicament destiné au traitement d'une maladie à médiation par le TNF chez un animal, sous réserve que ledit traitement ne comprenne pas le traitement topique d'une maladie inflammatoire, le traitement par inhalation d'affections allergiques des voies aériennes telles que l'asthme bronchique et la rhinite et le traitement oral et le traitement rectal de maladies allergiques du tractus intestinal telles que la calite ulcérative et la colite granulomateuse.

2. Utilisation suivant la revendication 1, dans laquelle la maladie à médiation par le TNF est choisie entre un choc septique, un choc endotoxique, une septicémie à germes Gram-négatifs ou un syndrome de choc toxique.

3. Utilisation suivant la revendication 1, dans laquelle la maladie à médiation par le TNF est choisie entre le syndrome d'immunodéficience aiguë (SIDA), le syndrome associé au SIDA (ARC) ou n'importe quel autre état pathologique associé à une infection par le VIH, une cachexie, une cachexie secondaire au SIDA, ou une cachexie secondaire à un cancer.

4. Utilisation suivant la revendication 1, dans laquelle la maladie à médiation par le TNF est choisie entre le paludisme cérébral, une infection virale par CMV, une infection par un virus grippal ou une infection par un virus de l'herpès.

5. Utilisation suivant la revendication 1, dans laquelle la maladie à médiation par le TNF est choisie entre le syndrome

de détresse respiratoire de l'adulte, le rejet d'allogreffes ou une maladie de résorption du tissu osseux.

6. Utilisation suivant la revendication 1, dans laquelle la maladie à médiation par le TNF est un état pathologique topique à médiation par une production excessive de TNF.

7. Utilisation suivant la revendication 1, dans laquelle la maladie à médiation par le TNF est choisie entre : l'arthrite rhumatoïde, la spondylite rhumatoïde, l'ostéo-arthrite, l'arthrite goutteuse et d'autres états arthritiques, une inflammation des articulations, un état pyrétique et la douleur.

8. Utilisation suivant l'une quelconque des revendications 1 à 7, dans laquelle R_1 représente un groupe cycloalkyle en C_3 à C_7 ou alkyle en C_1 à C_6.

9. Utilisation suivant l'une quelconque des revendications 1 à 8, dans laquelle R_2 représente un groupe alkyle en C_1 à C_6 et R_4 représente l'hydrogène, un groupe phényle, benzyle ou COR_6.

10. Utilisation suivant l'une quelconque des revendications 1 à 9, dans laquelle R_2 représente un groupe méthyle, R_5 représente l'hydrogène et X représente l'oxygène.

11. Utilisation suivant l'une quelconque des revendications 1 à 10, dans laquelle le composé consiste en 4-[3-cyclopentyloxy-4-méthoxyphényl]-2-pyrrolidinone.

12. Utilisation suivant l'une quelconque des revendications 1 à 11, dans laquelle le composé peut être administré par voie orale.